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(54) Title: RECEPTOR SELECTIVITY MAPPING		
(57) Abstract		
<p>A computer system comprising a first database containing records corresponding to a plurality of chemical compounds and records corresponding to biological information related to effects of the plurality of chemical compounds on biological systems and a second database containing records corresponding to a plurality of molecular targets. The computer system further comprises a third database containing records corresponding to tests of interaction between compounds in the first database and molecular targets in the second database, the tests including information on the effect that a compound from the plurality of compounds has on the interaction of a compound known to interact with a molecular target from the plurality of molecular targets and said molecular target. Means for setting an interaction test threshold corresponding to said effect and means for selecting the compound when its use results in a test meeting the interaction test threshold are also included in the computer system. A user interface is provided to allow a user to view the selected compound and to selectively view information from the first database, the second database, the third database as it relates to a compound record in the first database or as it relates to a molecular target in the second database.</p>		<pre> graph TD DS[Receptor Selectivity Database] --> SRD[Screening Results and Assay Database] SRD --> C[Chemical] SRD --> T[Target] SRD --> B[Biological] C --> S[Screening] T --> S B --> S S --> AR[Actual Testing] AR --> SR[screening results (e.g. % inhibition)] SR --> UDT[Use of Data Mining Tool or Database Query for Further testing] </pre> <p>The diagram illustrates the Receptor Selectivity Mapping system architecture. It features a central 'Receptor Selectivity Database' connected to a 'Screening Results and Assay Database'. This database contains three main components: 'Chemical', 'Target', and 'Biological'. The 'Chemical' component is associated with a value of 300, 'Target' with 400, and 'Biological' with 500. An arrow labeled 'new compounds' points to a 'Screening' module. The 'Screening' module is connected to an 'Actual Testing' box, which then leads to 'screening results (e.g. % inhibition)'. A dashed arrow from the 'Screening' module points to a box labeled 'Use of Data Mining Tool or Database Query for Further testing'.</p>

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RECEPTOR SELECTIVITY MAPPING

BACKGROUND OF THE INVENTION

The present invention relates generally to a combination of chemoinformatics and
5 bioinformatics and data on chemical-molecular target interactions to create multi-dimensional databases. More particularly, this invention relates to databases comprising chemical compound, molecular target, and biological or clinical information in which patterns or relationships of interactions between chemical compounds and molecular targets are determined and compared with other information in the database in order to
10 draw conclusions that are useful for drug discovery and development and for related areas.

The worldwide pharmaceutical industry spends more than \$30 billion a year on research and development, of which nearly one-third is spent on the discovery and early development phase, which is the period leading up to the selection of a drug candidate for preclinical and clinical development. Some critical steps in drug discovery include (1) sequencing DNA comprising segments of the human genome; (2) identification of genes within the genome that are associated with specific diseases or biological functions; (3) production of a protein such as a receptor or enzyme that corresponds to, or is encoded by, the functional gene and which then becomes a biological or molecular target for drug discovery; (4) screening a library of chemical compounds for activity against the
15 molecular target (high throughput screening); (5) screening the most potent active compounds against other biological targets (particularly other receptors or enzymes) to assess the compounds' selectivity or specificity for the intended biological/molecular target and potential to cause undesirable side effects through activity at other targets; (6) evaluating the most potent and selective compounds for their activity in a range of other
20 assays designed to measure such properties as toxicity, absorption, distribution, metabolism, excretion, *etc.*; (7) assessing the most promising compounds based on empirical judgments using the above information, and then sending that information to a chemical synthesis group to produce analogs (or modified but related chemical structures) of the initial active compounds; (8) retesting the chemical analogs through Steps (4), (5)
25 and (6), then repeating Step (7) until an optimized lead compound or series of compounds is identified; and (9) forwarding the optimized lead compounds to further preclinical and clinical testing.

Throughout this process of discovery and development, compounds go through successively narrower filters, and compounds are eventually selected for the more expensive phases of preclinical and clinical development. Unfortunately, the selection process often leads to preclinical testing and clinical testing of compounds that will fail at 5 these stages and never reach commercialization. These failures lead to extremely high average costs, estimated to exceed \$300 million, to develop and launch a new drug. If, however, the optimal drug candidate is correctly identified early in the discovery and development process and successfully passes preclinical and clinical testing, the actual cost to develop that drug may be reduced by as much as 75%. Clearly, a major goal of 10 pharmaceutical R&D should be to enhance the predictability of early drug development tests such as outlined above.

With the revolution of new techniques in biotechnology and the evolution of tools to automate many laboratory processes, two dominant trends have emerged in recent years that are having an important impact on pharmaceutical R&D. First, the number of 15 molecular targets (such as new receptors and enzymes) available for discovery screening programs continues to increase dramatically due to progress in sequencing the human genome. About 400 molecular targets have been explored for drug discovery; estimates of the number of potential molecular targets that may be elucidated from the human genome project range in the thousands to more than 10,000. Second, the size of chemical 20 compound libraries available for discovery screening programs has expanded nearly ten-fold (to more than a million compounds in many drug companies) due to automation and new technologies such as combinatorial chemistry. These two factors hold tremendous promise for new drug discovery, but they also create significant potential problems having adverse consequences on the cost of drug development. More targets and more 25 compounds will result in many more bioactive compounds being discovered, leading to greater difficulty in selecting the optimal drug candidates to advance to preclinical testing, as well as increased development costs due to more compounds entering preclinical and clinical testing and potentially more failures at these stages.

These factors point to an increased need for rapid, inexpensive, *in vitro* ("test-tube" 30 or microplate-based) assays for lead compound selection, optimization, and validation. Such rapid assays may help identify the most promising of these active compounds before

they enter the later, more expensive, stages of drug development. These factors further point to a need for more effective methods to manage and interpret the vast amount of data on genes and gene products (molecular targets), chemical structures, and screening results.

One application of *in vitro* assays that is gaining increased importance in

- 5 pharmaceutical R&D is "profiling." The assignee of this patent application pioneered the concept of profiling in the late 1980's. Drug companies are provided with an extraordinarily broad array of *in vitro* assays for characterizing the pharmaceutical activity and the potential side effects of compounds under development as new drugs. Currently there are more than 200 different assays that may be performed on a routine basis based on
- 10 molecular targets, called receptors and enzymes, that play a key role in a wide range of human diseases, including those associated with central nervous system disorders, immune diseases, pain and inflammation, infectious diseases, cancer, metabolism or growth factors, cardiovascular function, and the endocrine system. Pharmaceuticals accounting for more than one-half of the worldwide market function by interacting with cellular receptors. In
- 15 addition, many side effects of pharmaceuticals are also mediated through their interactions with receptors or enzymes.

Through profiling, a drug company's lead compounds, generally those entering preclinical development, are tested in a battery of receptor and enzyme assays.

- Information from the profiling process about interactions between the drug company's
- 20 compound and certain receptors is important for the process of lead compound optimization and selection and can suggest possible side effects or secondary therapeutic activities of the compound. This knowledge can potentially save the drug company millions of dollars in wasted time and expense during preclinical and/or clinical development of the compound.

- 25 While profiling services have been practiced for many years, the data generated from these tests are generally used empirically by drug companies. Most drugs, even highly selective drugs, interact with numerous receptors or other molecular targets. Interpreting data produced by profiling, therefore, depends on the experience and knowledge of the scientist from the drug company who reviews the data on both the
- 30 chemical structure of the compounds and the binding interactions of the compounds with specific receptors. Unfortunately, even the most experienced pharmacologist has an

incomplete knowledge of the interaction of different drug compounds with the broad range of receptors relevant to drug development.

- The need for more effective methods to manage, collate, interpret, and utilize the vast amount of data on genes and gene products (molecular targets), chemical structures, 5 and screening results has led to the creation of new opportunities in bioinformatics and chemoinformatics, or managing biological and chemical data. The stages of generating large pools of information for drug discovery can be broken down into (1) DNA sequences (code of genetic material or genes that are blueprints for the cell to make gene products or proteins); (2) functional genomics (process of conversion of DNA sequences to expression 10 of corresponding gene products or proteins via mRNA production, especially in response to drugs or changes in biological function); (3) proteomics (identification of the amino acid sequence and/or three-dimensional structure of gene products or proteins, such as receptors, for which the genes code); (4) small molecule pharmacology/toxicology (molecular binding or interactions between 15 gene products, like receptors, and small organic chemicals that are potential drugs); and (5) chemical structure (of small molecule, drug-like compounds).

- Databases for DNA sequences (Group 1) are well established and include GenBank, The Genome Center, and others. Similarly, databases of chemical structures (Group 5) are well known and provided by vendors such as MDL (Isis) and Oxford 20 Molecular. Databases for proteomics (Group 3), such as SWISS-PROT, ProLink, and PDB, are also being established. Each of these databases can be considered as one-component, in that they contain structural information and can be used to determine patterns in that one dimension or single component of structural or sequence information. Databases for Groups 2 and 4 are not well established, but should be valuable additions to 25 the information pool for drug discovery and development. These latter two forms of datasets would be two-component or two-dimensional in that they would contain data relating to the interaction between two structures, such as genes to proteins (Group 2) and proteins to chemicals (Group 4). Such relationship databases add a significant level of complexity compared with the one-component databases.

- 30 Partial databases or datasets for Group 4 relationships have been or are being established. For example, profiles of the binding of single compounds against a broad set

of receptor targets by the assignee for its clients is a partial dataset for Group 4-type databases. Similarly, data generated through high throughput screening projects in which thousands to hundreds of thousands of chemicals, such as might be contained in a chemical structure database (Group 5), are screened for activity against a specific receptor target (a single point in a Group 3 database), would represent a partial Group 4 database. Although such partial Group 4 datasets will be helpful aids for drug discovery and development, they suffer from two major drawbacks. First, they are directed toward specific two-component analyses, such as the binding selectivity of a single compound or limited set of compounds across a range of receptors (profile) or of many compounds at one receptor target (high throughput screening). In both cases, the breadth of the dataset is insufficient to allow statistical correlations to be drawn among a multiplicity of receptor targets and a multiplicity of chemical structures. Second, and importantly, these partial datasets are being generated on chemical compounds selected for their structural novelty and therefore proprietary potential as new drugs. Since these are novel compounds, there does not exist any biological information about the activity of these compounds in animals or humans. Such approaches therefore suffer the same limitations as the pharmacologist trying to empirically interpret the data of a profile, as described above.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to meet the foregoing needs by providing systems and methods for analyzing data relevant to drug discovery and development. A full-rank screening database including positive and negative data resulting from a large number of chemical compounds being tested against a large number of molecular targets is provided. The number of combinations of chemical compounds and molecular targets must be large enough such that a person of ordinary skill in the art of statistical or other data mining methods can use the screening database together with the corresponding chemical compound database and molecular target database to produce a reliable prediction of which chemical compounds are suitable for clinical testing and have an enhanced probability to be safe and effective drugs.

Specifically, systems and methods for meeting the foregoing needs are disclosed. The system includes a computer system comprising a first database containing records corresponding to a plurality of chemical compounds and records corresponding to

biological information related to effects of the plurality of chemical compounds on biological systems of humans or animals, and a second database containing records corresponding to a plurality of molecular targets. The computer system further comprises a third database containing records corresponding to tests of binding, reactivity, or other interactions between compounds in the first database and molecular targets in the second database, the tests including information on the effect that a compound from the plurality of compounds in the first database has on the interaction between a selected compound (e.g., a reference agent or standard) known to interact with a specific molecular target from among the plurality of molecular targets, said tests being performed for a plurality of the molecular targets in the second database. Means for setting an interaction test threshold corresponding to said effect and means for selecting the compound, sets of compounds, and/or information associated with such compound(s) when the results of the testing of the effect meet the interaction test threshold are also included in the computer system. A user interface is provided to allow a user to view and manipulate or analyze information from the first database, the second database, and the third database as it relates to one or more compound records in the first database and/or as it relates to one or more molecular target records in the second database, especially with respect to compounds, molecular targets, or other database records associated with results that meet the interaction test threshold(s).

Furthermore, the invention relates to using methods of statistical analysis and other data mining methods as applied to these multidimensional databases to determine correlations or patterns that are relevant to drug discovery and development.

Both the foregoing general description and the following detailed description provide examples and explanations only. They do not restrict the claimed invention.

25

DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate embodiments of the invention and, together with the description, explain the advantages and principles of the invention.

Fig. 1A illustrates a chemical compound table in the receptor selectivity mapping database according to one embodiment of the present invention;

Fig. 1B illustrates a snap-shot of a chemical compound record containing spatial coordinates of a compound in the receptor selectivity mapping database according to one embodiment of the present invention;

5 Fig. 2 illustrates several logical tables that may be used to access the molecular target information in the receptor selectivity mapping database according to one embodiment of the present invention;

Fig. 3 illustrates a biological information table in the receptor selectivity mapping database according to one embodiment of the present invention;

10 Fig. 4 illustrates the use of a receptor selectivity mapping database as part of a screening process according to one embodiment of the present invention;

Fig. 5A illustrates the use of a receptor selectivity mapping database as part of a screening process to discover and select new compounds as potential new drug candidates for further development;

15 Fig. 5B illustrates the use of a receptor selectivity database as part of a screening process to identify new targets as potential validated targets to use to discover new drug candidates for specific disease indications;

Fig. 6A illustrates the use of a database for predicting the drug potential of a new compound; and

20 Fig. 6B illustrates the use of a database to validate the disease relevance and/or the biological function of a new molecular target.

DETAILED DESCRIPTION

Reference will now be made to preferred embodiments of this invention, examples of which are shown in the accompanying drawings and will be obvious from the description of the invention. In the drawings, the same reference numbers represent the 25 same or similar elements in the different drawings whenever possible.

Systems and methods consistent with the present invention allow the analysis of data relevant to drug discovery and development, for example, for predicting the potential of a new compound's suitability for progression to preclinical and clinical tests with an enhanced probability of becoming a safe or effective new drug. For purposes of the 30 following description, the systems and methods consistent with the present invention are described with respect to a relational database containing multiple main tables and with the

use of the binding between chemical compounds and molecular targets as a measurement of the interactions between the two. The description should also be understood to apply in general for any database structure having multiple main components and to the measurement of any interactions between chemical compounds and molecular targets.

- 5 The present invention relates to the novel design, construction, and application of a database relating information-rich chemicals, molecular targets, especially proteins or other macromolecules, and biological activity of the chemicals. Furthermore, the present invention relates to the primary use of known drugs and drug candidates that have failed in clinical or preclinical trials as a source of the chemical library for the database, together
- 10 with preclinical or clinical data generated for such chemicals describing their side effects, mechanism of action and other medically relevant data. The present invention further relates to determining the binding or other interactions between the chemicals and the molecular targets in the database, then using methods of relationship analysis and data mining to correlate patterns of these interactions with specific biological activities that are
- 15 relevant to drug discovery and development, or with specific chemical structures, substructures, or other features of compounds exhibiting such interactions, or with biochemical, structural, or other features of molecular targets exhibiting such interactions. Examples of such data mining techniques can be found in the following references, which are incorporated by reference in their entirety:
- 20 a) Chen *et al.*, Recursive Partitioning Analysis of a Large Structure-Activity Data Set Using Three-Dimensional Descriptors, *Journal of Chemical Information and Computer Sciences*, October 1998;
- b) Hawkins *et al.*, Analysis of a Large Structure-Activity Data Set Using Recursive Partitioning, *Quant. Struct.-Act. Relat.*, 16:296-302 (1997);
- 25 c) DePriest *et al.*, 3D-QSAR of angiotensin-converting enzyme and thermolysin inhibitors; a comparison of CoMFA models based on deduced and experimentally determined active site geometries, *J. Am. Chem. Soc.*, 115:5372-84 (1993);
- d) Good *et al.*, in *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B. (eds.), VCH, New York, Vol. 7, pp 67-117 (1996);
- 30 e) Marshal *et al.*, in *Computer-Assessed Drug Design*; ACS Symposium Series 112; American Chemical Society: Washington, DC, 1979; pp 205--226;

- f) Moloc *et al.*, A three-dimensional structure activity relationships and biological receptor mapping, in *Mathematics and Computational Concepts in Chemistry*; Ellis Horwood; Chichester, 1985; pp 225-251;
- g) Mayer *et al.*, A unique geometry of the active site of angiotensin-converting-
5 enzyme consistent with structure activity studies, *J. Comput. Aided Mol. Des.*, 1:3-16.
(1987);
- h) Sheridan *et al.*, The ensemble approach to distance geometry: application to the
nicotinic pharmacophore, *J. Med Chem.* 29:899-906 (1986);
- i) Martin *et al.*, A fast new approach to pharmacophore mapping and its
10 application to dopaminergic and benzodiazepine agonists, *J. Comput. Aided Mol. Des.*,
7:83-102 (1993);
- j) Catalyst/Hypo Tutorial, version 2.0, BioCAD Corp. Mountain View, CA, 1993
- k) Sprague, P. W., Automated chemical hypothesis generation and database
searching with Catalyst, *Perspect. Drug Discov. Des.*, 3:1-20 (1995);
- 15 l) Barnum *et al.* Identification of common functional configurations among
molecules, *J. Chem. Inf. Comput. Sci.*, 1996, 36:563-71 (1996).
- m) HipHop Tutorial, version 2.3; Molecular Simulation Inc.; Sunnyvale, CA, 1995;
- n) Davies, K. and Upinn, R., 3D pharmacophore searching, *Net. Sci.*,
[\(<http://www.netsci.org/Science/Ceminform/feature02.html>\);](http://www.netsci.org/Science/Ceminform/feature02.html)
- 20 o) Golender, V. and Vesterman, B., APEX 3D expert system for drug design, *Net.
Sci.* (<http://www.awod.com/netsci/Science/Compchem/feature09.html>);
- p) Van Drie, J., Strategies for the determination of pharmacophoric 3D database
queries, *J. Comput. Aided Mol. Des.*, 11:39-52 (1997);
- 25 q) Van Drie, J. and Nugent, R., Addressing the challenges posed by combination
chemistry: 3D databases, pharmacophore; recognition and beyond, *SAR QSAR Environ.
Res.*, 9:1-21 (1998);
- r) Finn *et al.*, Pharmacophore discovery using the inductive logic programming
progol, in *Machine Learning, Special Issue on Applications and Knowledge Discovery*,
Kluwer Academic Publishers: Boston, 1998, pp 1-33; and
- 30 s) Jain *et al.*, Compass: a shape-based machine learning tool for drug design. *J.
Comput. Aided Mol. Des.*, 8:635-52 (1994).

The background section suggests that, contrary to standard operating procedures in the pharmaceutical industry, a Group 4 database should be established having more components than a two-component database, and that it should cover a substantial breadth of both receptor or enzyme targets and chemical compounds. By way of example, a three-
5 component database would be created by first selecting a broad set of chemical compounds that are rich in information of direct relevance to drug discovery and development. The most relevant information is often obtained by actual experience of testing such chemical compounds in humans through clinical trials and/or post-marketing surveillance or in animals through preclinical testing. Other relevant biological information may come from
10 natural products that demonstrate one or more observed bioactivities, as well as chemical reference standards that have been used in the industry to characterize the biology of receptors. Accordingly, one embodiment of information-rich chemical compounds selected for such a Group 4 database includes marketed pharmaceuticals, drugs that have failed in clinical or preclinical trials, bioactive natural products or natural extracts, and
15 reference agents used for receptor binding assays.

One may construct such a database using screening data obtained from the scientific literature. While this approach could yield partial datasets, it may have limitations. First, literature references generally provide only positive information (*e.g.*, reports of inhibition of binding of a specific compound to a specific receptor) and not
20 negative data (*e.g.*, a lack of inhibition of binding and therefore lack of activity). In determining useful comparisons of information, negative data can be as valuable as positive data. Furthermore, certain statistical analyses may not be applicable to datasets that lack completeness of both positive and negative data. Second, separate quantitative reports of binding data for one compound against a receptor in one article vs. reports of
25 binding data for a second compound at the same receptor may not be comparable because of variations in the way the assays were performed. Therefore, one embodiment for creation of a Group 4 three-component database would be to screen a broad array of compounds through a broad array of receptor or enzyme targets in order to obtain consistent comparative results and ensure the collection of both positive and negative data.

30

The Chemical Compound Component: Selection of Chemical

Libraries and Inclusion of Chemical Data

- The present invention relates to databases that contain, as one component, chemical compounds about which information is known concerning biological activity relevant to pharmaceutical research and development. The biological activity information may be included in the chemical compound database or table.

For example, these information-rich chemicals include:

- (a) Compounds that are pharmacological reference agents or reference standards for measuring the interaction or molecular binding between unknown chemical compounds and a specific molecular target, such as a receptor or enzyme. Examples of such reference compounds include those compounds that are used for characterizing binding interactions between test compounds and molecular targets including receptors or enzymes. Other reference agents could include chemicals selected from the catalog of Research Biochemicals Inc. (RBI), a unit of Sigma Aldrich Corp., and from other sources that are well known in the industry. These pharmacological reference compounds often have been tested previously and/or marketed as pharmaceuticals or are natural products with characterized biological activity and therefore may overlap with compounds in the following three categories;
- (b) Compounds that are known pharmaceuticals that are currently or have previously been marketed for clinical use, and for which there is a substantial amount of biological information available. These compounds are well-known and are listed in publications available from U.S. government agencies such as the Food and Drug Administration (FDA), as well as publications by private or non-profit organizations. One such publication by a non-profit organization is the United States Pharmacopeial Convention Inc.'s *USP DI Series*, including *Volume I. Drug Information for the Health Care Professional*, which is updated monthly by *USP DI Update*. As new drugs are approved for marketing, they would be included in this category. Marketed pharmaceuticals or drugs approved by the FDA or equivalent foreign regulatory bodies are a matter of public record so that one normally skilled in the art can easily identify chemical compounds that would be included in this category;
- (c) Compounds that have been approved for testing in humans, such as compounds that had been granted IND (Investigational New Drug) status, as potential drugs but that

- failed to achieve sufficient efficacy or safety in clinical trials to gain approval from the FDA or otherwise did not reach the status of marketed pharmaceuticals. Compounds in this category may also include those compounds that have been approved by the FDA for commercialization but that have later been withdrawn from the market. These compounds
- 5 also would have a significant amount of biological information available and would be especially useful for purposes of this invention. The identity of failed drugs can be obtained from numerous sources, including public announcements by drug and biotechnology companies, publications such as the "Pink Sheets," and lists maintained by the FDA; and
- 10 (d) Compounds that are obtained from natural sources such as plants, microorganisms, animals, *etc.*, that exhibit biological activity. These natural products may include toxins, antimicrobial agents, behavioral modifiers, defensive agents, and other categories of compounds that provide information relevant to drug discovery and development. The identity of natural products can be found in numerous publications,
- 15 including but not limited to, the RBI catalog and Sigma Aldrich catalog of chemical compounds.
- For each compound included in the database, chemical structure, chemical formulae, physical-chemical characteristics, chemical space coordinates or other chemical structure descriptors (*e.g.*, Smiles codes), solubility, and other relevant data, to the extent
- 20 such information is available, are entered into fields in the database. Those skilled in the art would recognize other parameters that might be included. Chemicals can be organized by chemical structure relatedness in the database or by other relationships.
- Fig. 1A illustrates a chemical compound table 300 in a relational database system. The table 300 lists a number of chemical compounds and includes records (rows 1-N) of a
- 25 number of compounds N. For each compound there may be a number of corresponding columns 301-307 containing information related to the compound. For example, in Fig. 1A column 301 contains the name of the compound; column 302 includes the compound type (*e.g.*, compounds that have been approved for testing in humans, *etc.*); column 303 includes information related to the chemical structure, for example, a hyperlink that brings
- 30 up a screen containing a drawing of the structure (see snap-shot 310 in Fig. 1B); column 304 includes the chemical formula for the compound; column 305 includes information

about the physical-chemical characteristics of the compound; column 306 includes chemical space coordinates of the compound; and column 307 includes solubility information of the compound.

- Additional columns may be added in order to include other relevant data related to
5 each chemical compound 301 listed in the table 300. These additional columns may include biological activity of the compound, rendering the chemical compound database a two component database (see also database 500).

Fig. 1B illustrates a snapshot 310 that may include information corresponding to a record in the table 300. For example, the chemical formula 304 of a compound may be
10 included in the snapshot of the record as well as the compound's structure 303.

The Molecular Target Component: Selection of Receptors, Enzymes, and Other Molecular Targets and Inclusion of Molecular Target Data

Molecular targets such as receptors, enzymes, other proteins, nucleic acids,
15 carbohydrates, and other macromolecules relevant to drug discovery and development, are representative of the second component of the databases comprising this invention. In one embodiment of this invention, receptors and enzymes are the principal molecular targets. Receptors mediate much of the molecular communication among cells and organs in the body. Enzymes often amplify such communications through, for example, secondary
20 messenger systems and cell signaling pathways.

Receptors include classical families of receptors such as dopamine receptors, serotonin receptors, opiate receptors, muscarinic receptors, adrenergic receptors, adenosine receptors, etc. These receptor groups include subtypes of the receptor type (such as dopamine-1, dopamine-2, dopamine-3, dopamine-4, and dopamine-5 receptors). Certain
25 subtypes have further variations (such as dopamine 4.2, dopamine 4.4, and dopamine 4.7) or can have different forms (such as dopamine 2 short and dopamine 2 long). Splice variants of receptors can also occur, as can mutations in the genes encoding specific receptors which might lead to a subset of a population that has a receptor with slightly different binding affinity for drugs or other compounds compared with the normal receptor
30 type. Receptors can be grouped by family, superfamily, or subfamily. Some groupings include G-Protein Coupled Receptors, 7 transmembrane receptors, nuclear receptors, etc.

Receptors can be grouped by the degree of homology of the DNA sequence of their corresponding genes. Receptors can also be grouped by their amino acid sequence and related three-dimensional conformations. Receptors can be classified by their location of expression in tissues or across different cell types.

- 5 Enzymes can include proteases, carbohydrateases, kinases, phosphatases, DNA-modifying enzymes, transferases, P450's, and others known to those skilled in the art.

- Other receptors, receptor sources, and corresponding assays are constantly being developed by the assignee to be added to the content of the database. Additional receptors and receptor assays are well known to those skilled in the art. Lists and descriptions of
10 certain receptors relevant to drug discovery and development can be found in numerous publications known to those skilled in the art. These publications include the RBI Handbook of Receptor Classification and the IUPHAR receptor classification book. Furthermore, as new receptors and receptor subtypes are discovered, they can be added to the content of the database.

- 15 Enzymes and enzyme assays are well known to those skilled in the art. Lists and descriptions of certain receptors relevant to drug discovery and development can be found in numerous publications known to those skilled in the art.

- Fig. 2 illustrates tables 400, 410, and 420 forming part of a relational database system which may be used to access molecular target information. Table 400 lists the
20 targets and includes records (rows 1-M) of a number of targets M. Column 401 lists the names of the target, while column 402 specifies the target type corresponding to each target name.

- Table structures may vary according to the target type specified in column 402. Table 410 includes information about those targets listed in table 400 which are classified
25 as receptors. Records from table 410 may be accessed by querying the database for a particular receptor name. The receptor names found in table 410 may be accessed, in turn, by querying table 400 for those target names for which column 402 reads "Receptor."

- In table 410, column 411 contains the name of the receptor, which is also the name of the target in column 401 in table 400; column 412 includes receptor family information;
30 column 413 includes receptor superfamily information; column 414 includes receptor subfamily information; column 415 includes the information about the degree of

homology of the DNA sequence of corresponding genes; and column 416 includes information on amino acid sequence. The amino acid sequence is one of a number of molecular descriptors that may be included in the database. Other molecular descriptors 417, for example, could include hydropathy plots corresponding to the amino acid 5 sequence. Because the molecular target database represented by tables 400, 410, and 420 includes target information and associated biological information related to the targets is included in the database (see table 600), this database may be considered a two-component database. The columns shown are illustrative of the types of information that may be included in the database and should not be construed as limiting the invention.

10 Table 420 includes information about those targets in table 400 that are classified as enzymes. Records from table 420 may be accessed by querying the database for a particular enzyme name. The enzyme names found in table 420 may be accessed, in turn, by querying table 400 for those target names for which the target type column 402 reads "Enzyme."

15 In table 420, column 421 contains the name of the enzyme, which is also the name of the target in column 401 of table 400 and column 422 includes enzyme type information. Column 423 is labeled as "Other relevant information" and is included in the table for purposes of illustrating that additional columns may be added to table 420 depending on other enzyme information that a user of the database might want to access, 20 including amino acid sequence and molecular descriptors.

Although only tables 410 and 420 are shown to describe the access of molecular target information by using the target type, additional tables may be added to the relational database system corresponding to the number of molecular target types available in the database.

25

**The Biological Information Component: Selection of
Biological/Clinical Information Parameters**

Biological information forming part of the database includes material that would 30 relate to side effects, mechanism of drug action, metabolism of a drug, toxicity, adsorption, distribution, and excretion, for example. This information is available on FDA-approved labels of marketed drugs, or from literature sources and publications for drugs that have

- failed in clinical trials. Examples of some specific parameters are toxicity, LD₅₀, LD₅₀/ED₅₀, teratogenicity, mechanism of toxicity, target organ for toxicity, in vitro toxicity battery, induction of apoptosis, bioavailability, absorption, blood-brain barrier, oral absorption, mucosal absorption, % absorbed, distribution, blood protein bound, half-life, 5 onset of action, duration of action, peak concentration in blood, metabolism, major pathway, minor pathway, active metabolites, excretion, primary excretion mode, secondary excretion modes, *in vivo* effects, therapeutic indication, animal behavioral effects, side effects, primary known target, other organ/system targets, and known receptor interactions.
- 10 Fig. 3 shows table 500 which includes some of the biological information parameters mentioned above. Table 500 comprises N rows (1 through N) which correspond to all the possible chemical compounds in the first database. Column 501 includes the compound name; column 502 includes the therapeutic indication (for marketed or failed drugs); column 503 includes toxicity information; column 504 includes 15 side effects information; and column 505 includes information on the mechanism of drug action. Table 500 would be associated with table 300, for example, to form a two-component chemical compound and biological activity table.

Fig. 3 also shows table 600, which includes biological information parameters associated with the molecular targets in the database. Table 600 includes P rows (1 20 through P) which correspond to all the possible targets in the second database. Column 601 includes the target name; column 602 includes the therapeutic indication (for marketed or failed drugs); column 603 includes toxicity information; and column 604 includes side effects information. Similarly, table 600 would be associated with table 400, for example, to form a two-component molecular target and biological activity table. Tables 500 and 25 600 together may be a full-rank database (e.g., including all possible combinations between compounds and molecular targets in a relational database system) including molecular target information, chemical compound information, and biological activity information associated with each of the molecular targets and with each of the chemical compounds, and may be considered a multidimensional database. Additional columns 30 may be included in tables 500 and 600 without departing from the invention.

Determining Binding Information

A key feature of this invention is the establishment of several components of information which, by way of illustration, comprise chemicals, molecular targets, and biological information, and measuring the binding, reactivity or other interactions between

5 the chemicals and molecular targets. This binding or reactivity information can then be related back to the known biological information in order to distinguish patterns and relationships that can be used for drug discovery and development. An important aspect of this invention is to generate broad and consistent binding or reactivity data between the chemicals and molecular targets in order to provide as complete a dataset as possible in

10 order to be able to identify relevant patterns or relationships and to provide both positive and negative binding or reactivity information for the datasets. In one embodiment, the binding data is established as a numerical descriptor that either satisfies or does not satisfy a threshold set, for example, for a specific molecular target or set of molecular targets.

The numerical descriptor may relate to the activity or lack of activity for each compound

15 and each receptor or other molecular target measured at a concentration deemed near the appropriate threshold for relevance to the biological system or biological information set. For example, chemicals can be tested at 10^{-5} M (10 micromolar) for their ability to inhibit binding at a threshold of 30% between a receptor and its specific reference compound. Other initial concentrations or percentage inhibition thresholds can be selected. Also, in

20 one embodiment, those chemicals that demonstrate inhibition of binding above the threshold in the initial yes/no testing are further tested for the potency of the binding inhibition. These active chemicals are tested at a series of concentrations that might, for example, include tests at 7-14 different concentrations within the range of 10^{-5} to 10^{-9} M, such that an IC_{50} and/or Ki value can be determined for the active compound at the specific

25 receptor. Fewer or more concentrations may be used for such determinations and concentrations above or below 10^{-5} to 10^{-9} M may be required. These data then yield a matrix of relative degree of activity or relative potency for each active compound at each molecular target.

In order to generate these screening data, chemicals are first solubilized in a

30 suitable solvent system, such as 4% DMSO, although other concentrations of DMSO and other solvents are also acceptable. These chemical stock solutions are then diluted to the

appropriate concentration and made available as repositories. For each assay measuring the interactions between the chemical and molecular target, the reagents and protocols for the assay will vary. Each such assay needs to be characterized and routinely established for consistency. Appropriate controls need to be run each time the assay is performed.

- 5 Any assay format that can generate the desired type and accuracy of information can be used. Numerous assay detection systems, such as radioactive labels, fluorescence, fluorescence polarization, time-resolved fluorescence, fluorescence correlation spectroscopy, chemiluminescence, UV absorption, colorimetric, etc., can be used.

In one embodiment, a receptor-binding assay or enzyme activity assay is used to
10 generate data on molecular interactions. As an example, for a receptor binding assay, chemicals from a repository are tested for their ability to inhibit the binding interaction between the receptor and a reference agent selected for that receptor. The receptor may be derived from a tissue source, such as animal or human tissue, or from a cell line expressing the receptor, or from a transfected cell line containing the gene for the receptor. The
15 receptor source is prepared for the assays, for example, by preparing a membrane fraction containing the receptor. Alternatively, the receptor may be partially purified. The reference compound, or ligand, is preferably selected for its potent and/or specific binding to the specific receptor and may have a radioactive tracer such as Iodine-125 or tritium or carbon-14 or other marker to enable a bound ligand to be distinguished from an unbound
20 ligand. Coincident with testing the chemicals for binding data to include in the database, positive and negative controls are run, as is a reference curve with varying concentrations of the reference (radio)ligand to ensure the quality of the assay run.

A plurality of methods and systems may measure the interactions between targets and compounds as would be recognized by a person of ordinary skill. The radioligand,
25 receptor preparation, and test compounds are incubated together for an appropriate time, in an appropriate buffer, and at an appropriate temperature, often with the objective of reaching equilibrium of the binding reactions. The amount of bound versus unbound radioligand is determined by a separation step, such as filtration, or by use of a method, such as SPA (scintillation proximity assay), and measured by liquid scintillation or gamma
30 counting. The amount of specific binding of the test compound is then determined by

comparing assay results for the test chemical(s) vs. the positive and negative controls. The per cent inhibition of the test chemical(s) is calculated from these data.

Fig. 4 shows table 200 as an illustration of a screening results and assay database in which, for example, chemical compounds included in database 300 (comprising 1 to N
5 chemical compounds) are tested for their effect against molecular targets included in database 400. Numerous forms of table 200 are possible. For example, in table 210 screening results are entered in a "yes" or "no" entry with respect to whether the screening result for each of a plurality of chemical compounds tested against each of a plurality of molecular targets was above or below the selected threshold test result for each set of
10 determinations.

As another example, in table 220 screening results are entered as a numerical descriptor identifying the potency or magnitude of the binding or other effect (e.g., the Ki for chemical:receptor interactions) for each of a plurality of chemical compounds tested against each of a plurality of molecular targets. In a preferred embodiment, all such matrix
15 points for chemicals x targets in tables 210 and 220 are determined and entered into the database such that a full-rank dataset is derived. The screening results and assay database 200 may also include other measurements of chemical:target interactions, including raw data of screening results and measurements derived from the raw data, assay protocols and performance characteristics, and other relevant information.

20 Figs. 5A and 5B illustrate the use of a database 100, here shown as a receptor selectivity database, by way of example, as part of a screening process to discover and select new compounds as potential new drug candidates for further development (Fig. 5A) or new targets as potential validated targets to use to discover new drug candidates for specific disease indications (Fig. 5B). The database 100 may include a chemical
25 compound component 300; a molecular target component 400; biological information components 500 and 600; and a screening results and assay database 200.

A new compound or set of compounds is introduced to a screening process 102 for determining whether it is effective in inhibiting the binding of a specific chemical compound (e.g., a reference agent) and a molecular target (see Fig. 5A). The screening
30 process may use target information from the molecular target component 400.

The results of the screening process 102 may be stored in an intermediate database or entered into the screening results and assay database 200 of the receptor selectivity database 100. The results may also be stored in the biological information database 500 as particular parameters (*e.g.*, cytotoxicity, *etc.*) as well as in the chemical compound database 300 (*e.g.*, name of the compound, *etc.*).

5 The complete set of results from the screening process 102 may be stored in the screening results and assay database 200. The database 200 may be queried for those new compounds that exhibit an inhibitory effect on the binding of molecular targets and chemical compounds (*e.g.*, reference agent) so that those new compounds can further be tested.

10 Alternatively, a new molecular target, such as, for example, an "orphan" receptor about which the structure is known but the function or disease relevance is not known, is introduced to a screening process to be to be tested against the chemical compounds in the chemical compound database 300 (see Fig. 5B). Results of the screening process, 15 including identification of chemicals that interacted with the new molecular target, are incorporated into the screening results database 200. Queries are made within database 100 to determine further steps to identify the function of the new molecular target and/or validate the disease relevance of the new target.

Fig. 6A illustrates the use of the database 100 for predicting the drug potential of a 20 new compound. A table 710 relies on information from the chemical compound (300), molecular target (400), biological information (500 and 600), and screening results (200) databases. The table 710 is filled in with information from one or more of these databases (or tables) by executing an automatic query script to retrieve the information once a user provides the database 100 with information about a new chemical compound.

25 The query script used for the creation of table 710 may select chemical compounds from the chemical compound database 300 upon receiving the new compound information. The selection may be based on similar characteristics, such as chemical structure or other properties, between the new compound and the compounds already included in the database 300.

30 After the selection of chemical compounds, the query script selects targets from the target database 400 that are known to react (*e.g.*, bind) with the selected compounds.

Finally, the combination of selected chemical compounds and selected molecular targets may be used for querying the biological information databases 500 and 600 and inserting biological information corresponding to chemical compound-molecular target pairings into table 710. Alternatively, the user may enter a specific biological information category of 5 interest (e.g., toxicity) so that the biological information included in table 710 is limited to that category.

The table 710 may be queried by the user to produce information relevant to the predictability of the potential use of the new compound as a drug. An example of this would be a query of the molecular targets known to react with chemical compounds 10 associated with the new compound, and the known side effects produced by the chemical compounds when combined with the retrieved targets.

Fig. 6B illustrates the use of the database 100 to validate the disease relevance and/or the biological function of a new molecular target using an approach similar to that used to predict the drug potential of a new compound, but with the data inputs and queries 15 shown in Fig. 6B.

All patent, patent applications, and publications mentioned are incorporated by reference in their entirety into this application.

The foregoing description of embodiments of the present invention provides an exemplary illustration and description, but is not intended to be exhaustive or to limit the 20 invention to the precise form disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention.

WHAT IS CLAIMED IS:

1. A computer system comprising:
 - a first database containing records corresponding to a plurality of chemical compounds and records corresponding to biological information related to effects of such chemical compounds on biological systems;
 - 5 a second database containing records corresponding to a plurality of molecular targets;
 - a third database containing records corresponding to tests of interactions between compounds in the first database and molecular targets in the second database, the tests including information on the effect that a compound from the plurality of compounds has on the interaction of a compound known to interact with a molecular target from the plurality of molecular targets and said molecular target; and
 - 10 a user interface allowing a user to view the selected compound and to selectively view information from the first database, the second database, and the third database as it relates to a compound record in the first database or as it relates to a molecular target in the second database.
2. The computer system of claim 1, wherein the interaction includes binding and the effect includes inhibitory effect.
3. The computer system of claim 1, wherein the chemical compounds include compounds with no known biological activity or that have failed in tests.
- 20 4. The computer system of claim 1, wherein the chemical compounds include compounds tested in animals.
5. The computer system of claim 1, wherein the chemical compounds include compounds known to have an effect on the environment.
- 25 6. The computer system of claim 1, wherein the chemical compounds include pharmacological reference agents.
7. The computer system of claim 1, wherein the chemical compounds include known pharmaceuticals in the market for clinical use for which there is a substantial amount of biological information available.
- 30 8. The computer system of claim 1, wherein the chemical compounds include compounds approved for testing in humans.

9. The computer system of claim 1, wherein the chemical compounds include compounds obtained from natural resources that exhibit biological activity.
10. The computer system of claim 1, wherein the molecular targets include receptors.
- 5 11. The computer system of claim 1, wherein the molecular targets include enzymes.
12. The computer system of claim 1, wherein the molecular targets include nucleic acids.
13. The computer system of claim 1, wherein the molecular targets include carbohydrates.
- 10 14. The computer system of claim 1, wherein the records of the first database corresponding to a plurality of chemical compounds are organized in categories related to the description and properties of the compounds.
- 15 15. The computer system of claim 14, wherein the categories include:
 - compound name;
 - compound type;
 - physical-chemical characteristics;
 - chemical space coordinates or structural descriptors; and
 - solubility.
- 20 16. The computer system of claim 1, wherein the first database includes a natural product database.
17. The computer system of claim 1, wherein the first database includes a failed drug database.
- 25 18. The computer system of claim 1, wherein the first database includes a chemical registry database.
19. The computer system of claim 1, wherein the second database includes a three-dimensional structure database.
20. The computer system of claim 1, wherein the second database includes a sequence/mutation database.
- 30 21. The computer system of claim 1, wherein the second database includes a genomic database.

22. The computer system of claim 1, wherein the records in the third database corresponding to biological information related to the chemical compounds effects on the biological targets, are organized in categories that include:

- compound name;
- 5 target name;
- toxicity;
- side effects; and
- mechanism of drug action.

23. The computer system of claim 1 further comprising means for setting an interaction test threshold corresponding to said effect and means for selecting the compound when its use results in a test meeting the interaction test threshold.

24. A method for analyzing data relevant to drug discovery and development comprising:

- selecting chemical compounds from a first database containing records corresponding to a plurality of chemical compounds;
- selecting molecular targets from a second database containing records corresponding to a plurality of molecular targets;
- producing information corresponding to the interactions between each of the selected chemical compounds and each of the selected molecular targets;
- 20 selecting a biological activity from a third database containing records corresponding to biological information related to effects of chemical compounds on biological targets; and
- using the produced information to correlate patterns of interactions between chemical compounds and molecular targets associated with the selected biological activity.

25. The method of claim 24, wherein the step of producing information includes the steps of:

- generating binding data of the binding between each of the selected chemical compounds and each of the selected molecular targets by monitoring the inhibitory effect
- 30 that an unknown compound has on said binding;
- setting a binding test threshold corresponding to the inhibitory effect; and

generating information on the combination of unknown compound, molecular target, and chemical compound that meets or fails to meet the binding test threshold.

26. The method of claim 25, wherein the binding data comprises positive and negative binding information.

Compound Name	Type	Chemical Structure	Chem Formulae	Physical-chemical characteristics	Chemical space coordinates	Solubility
1						307
2						306
3						305
4						304
5						303
6						302
N						301

FIG. 1A

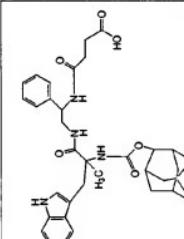
Chemical Snap-shot -	General Description
Name & Trade Names	Known Target(s) & Activities Receptor Selectivity Mapping Pharmacology & Toxicology CAS M.W. Formula: $C_{39}H_{42}N_4O_4$
 <p>303</p> <p>304</p>	

FIG. 1B

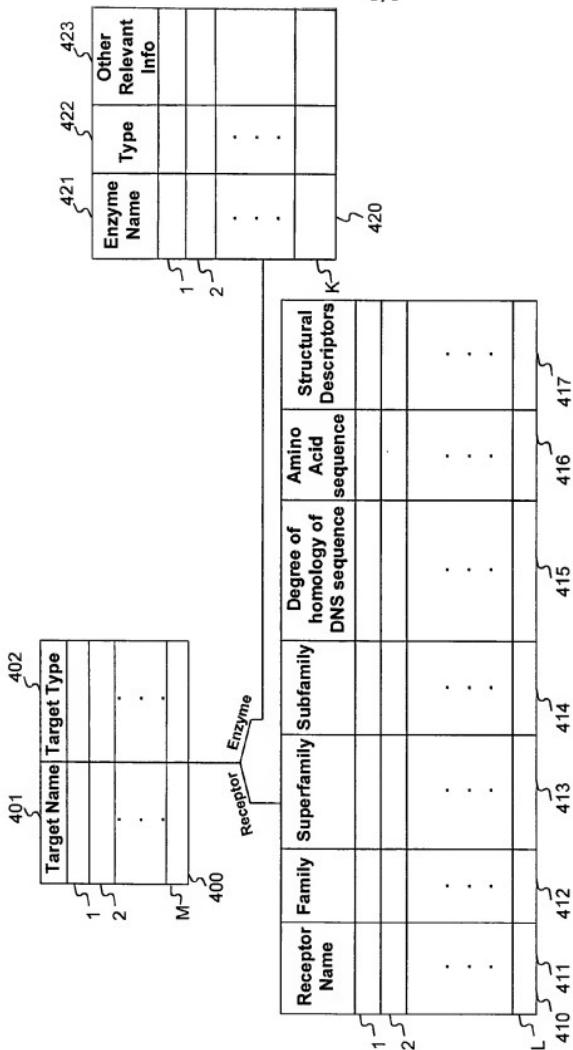


FIG. 2

Biological/Clinical Information Tables

Compound Name	Therapeutic Indication	Toxicity	Side Effects	Mechanism of drug action	505
Comp 1					504
Comp 2					503
:					502
Comp N					501

Target Name	Therapeutic Indication	Toxicity	Side Effects
Target 1			
Target 2			
Target P			

FIG. 3

Compound Name	Target Name	First Pass	Second Pass	IC_{50}/K_i	Threshold	Assay Condition-1
Comp 1						
Comp 2						
:						
Comp N						

200

\sum

Compound Name	Target Name	Target P		Target P
		Target 1	Target 2	
Comp 1	X	X	X	Y
Comp 2	X	X	X	Y
:	X	X	X	Y
Comp N	X	X	X	Y

220

\sum

\sum Y = screening result
(above or below threshold)

\sum X = screening result
(above or below threshold)

Y = screening result
(potency, e.g., K_i)

FIG. 4

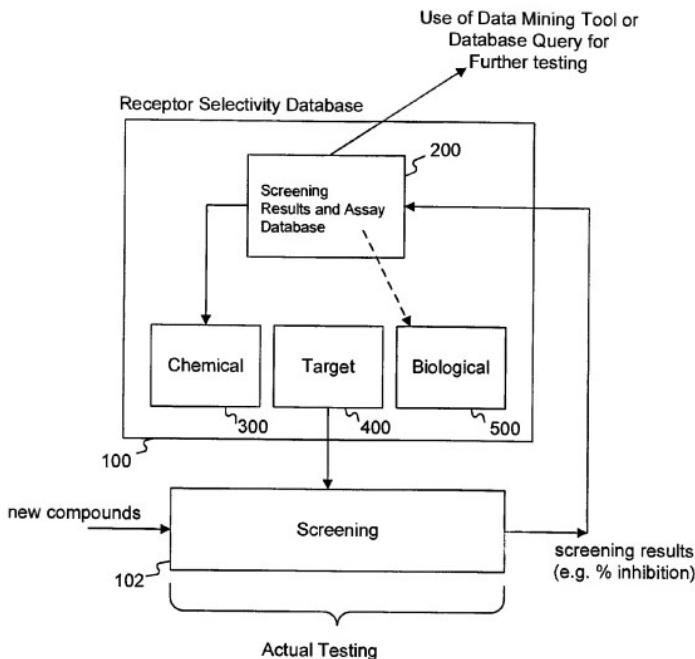


FIG. 5A

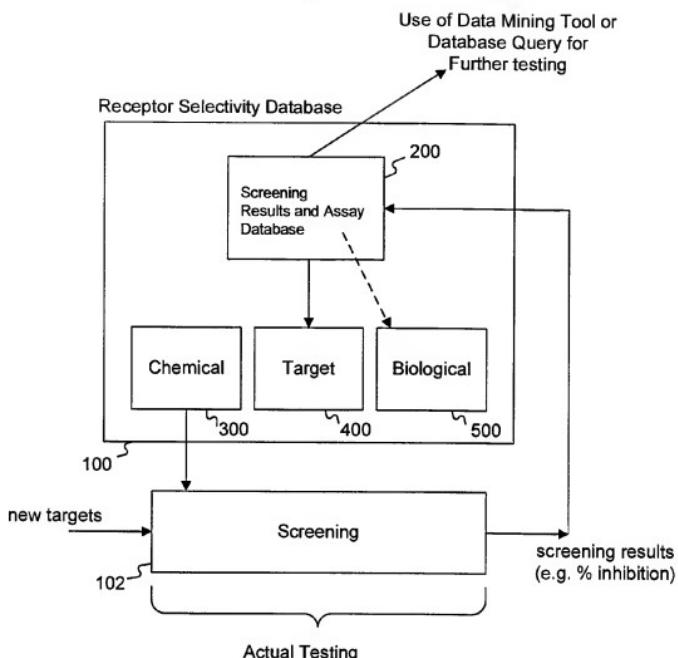


FIG. 5B

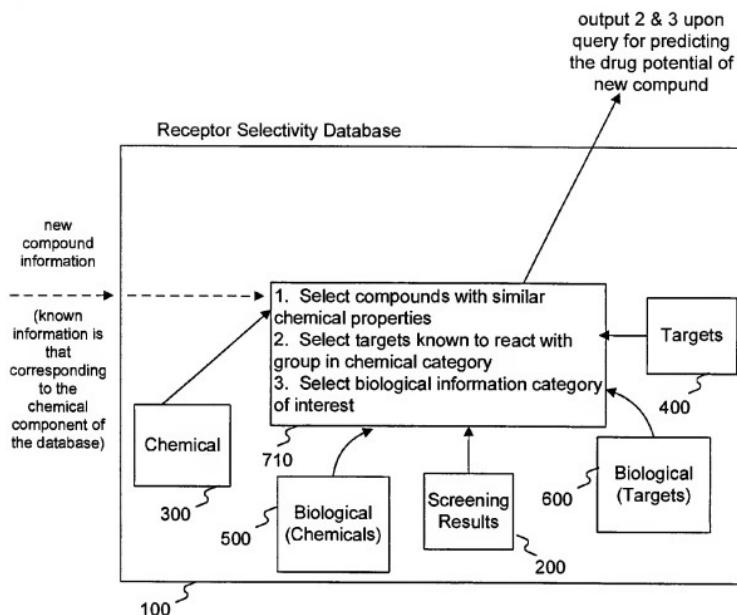


FIG. 6A

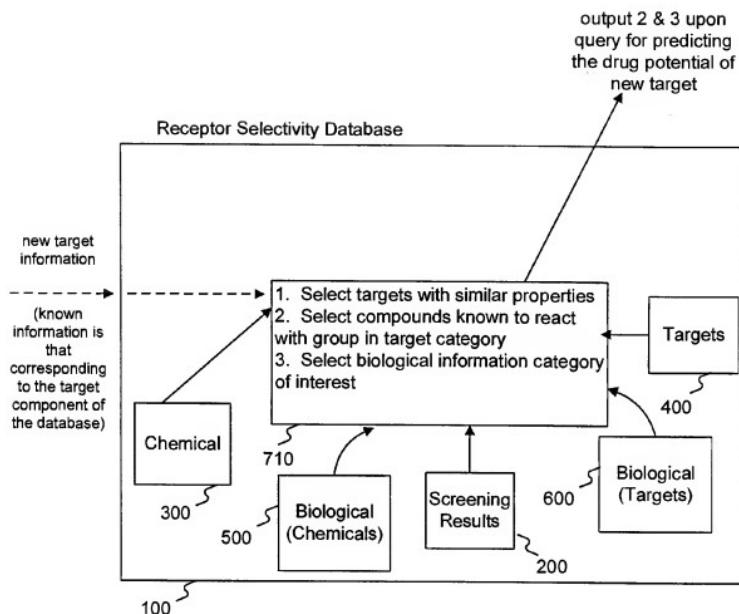


FIG. 6B